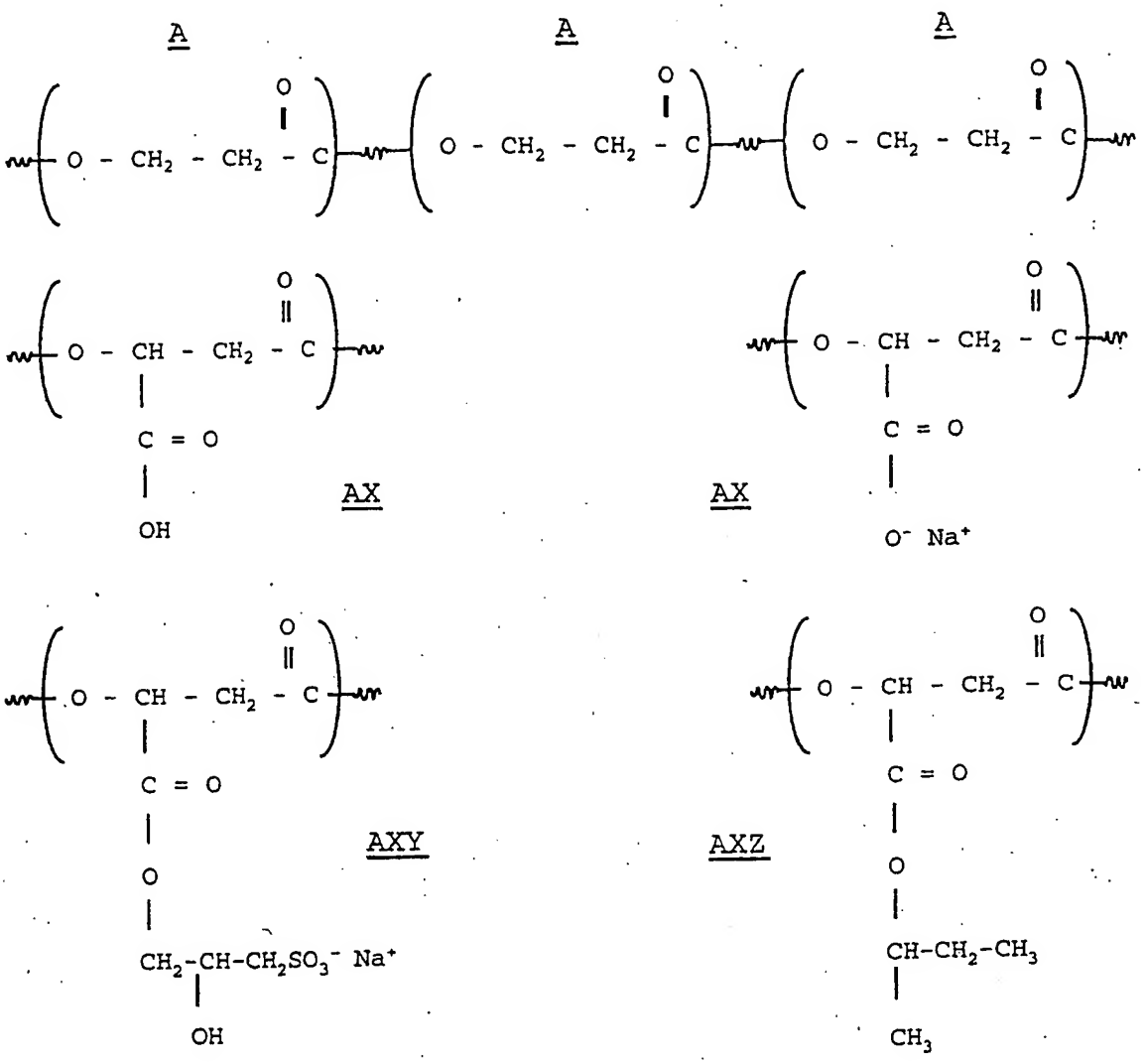
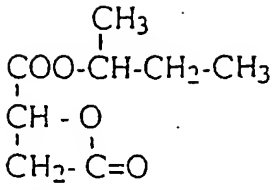
Fig.1



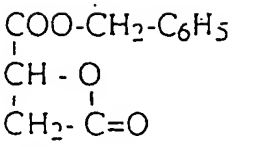
THE β-MALIC ACIDS

Fig.2



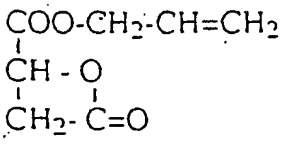
1.MLABu

2-BUTYL MALOLACTONATE



2.MLABe

BENZL MALOLACTONATE



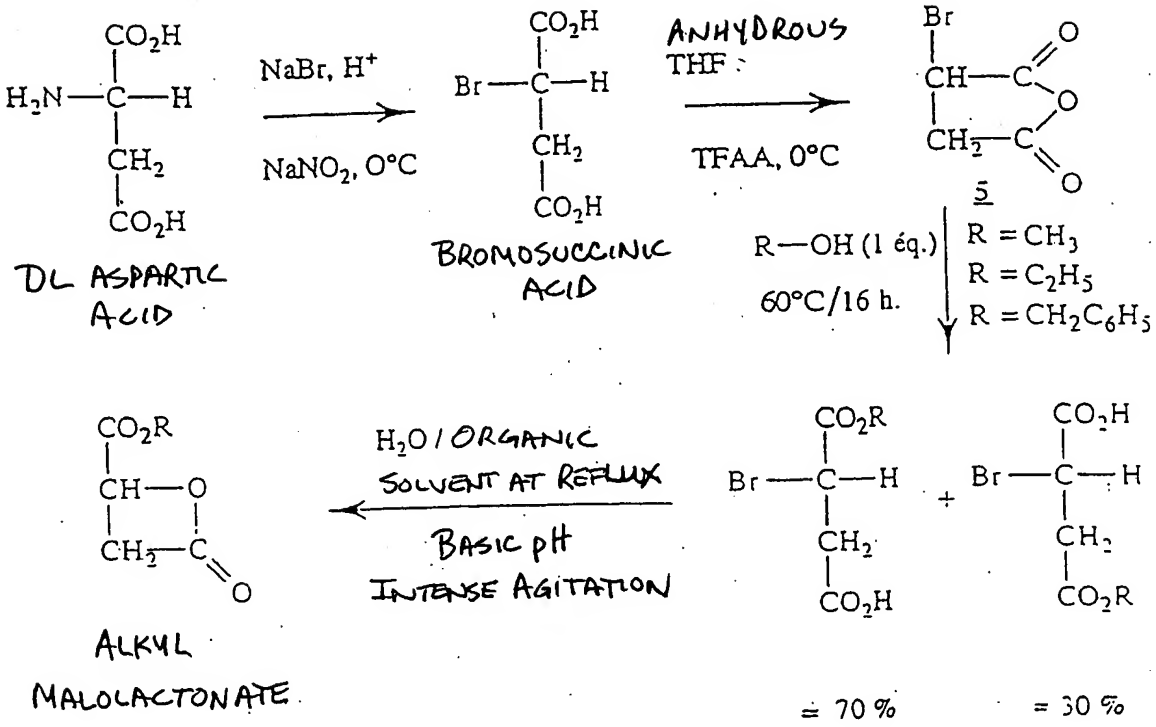
3.MLAAl

ALLYL MALOLACTONATE

STRUCTURE OF THE

3 β-LACTONES

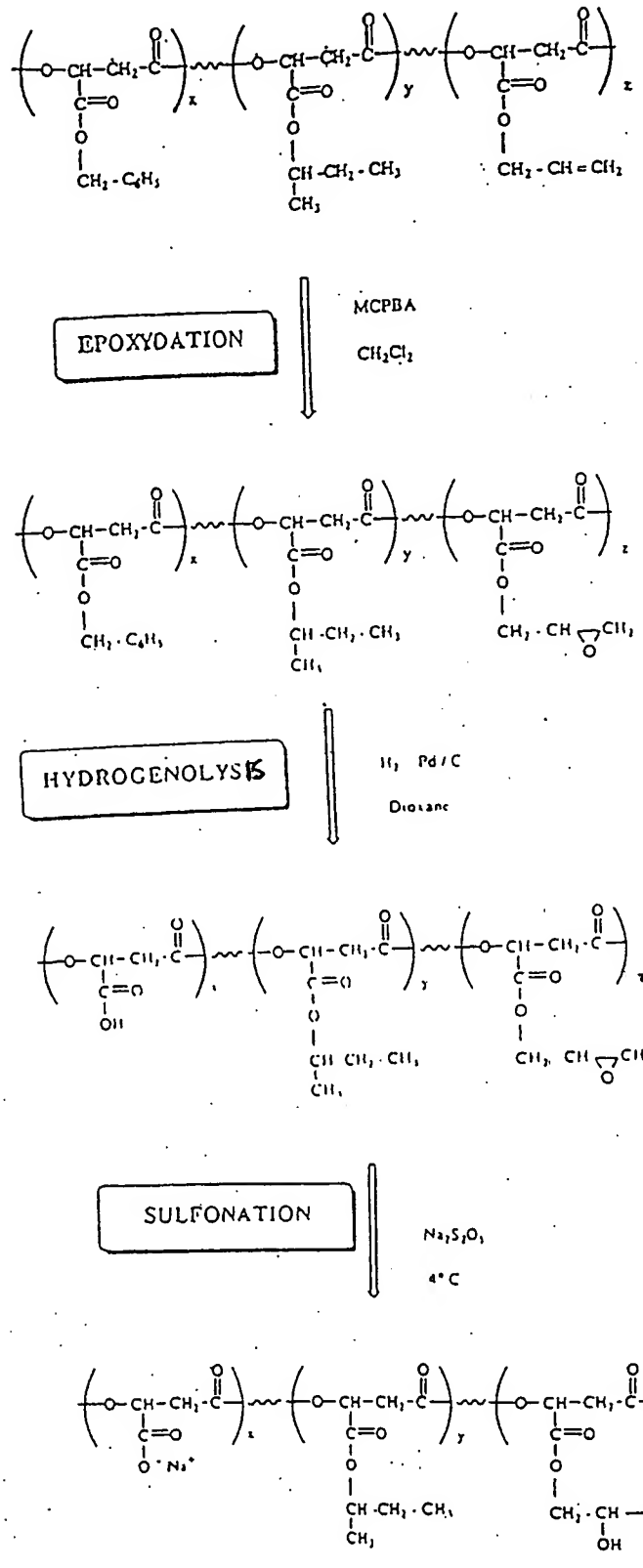
FIG.3



SYNTHESIS OF ALKYL MALOLACTONATE FROM DL-ASPARTIC ACID

R = -CH(CH3)-CH2-CH3, BENZYL MALOLACTONATE OR -CH(CH3)-CH2-CH3 (2-BUTYL MALOLACTONATE) OR -CH2-CH=CH2 (ALLYL MALOLACTONATE).

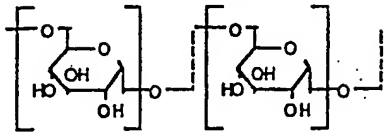
Fig.4



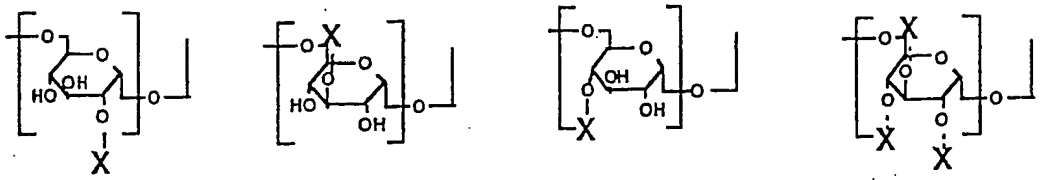
SYNTHESIS OF DERIVATIVES OF POLY(β-MALIC ACID)

Figure 5

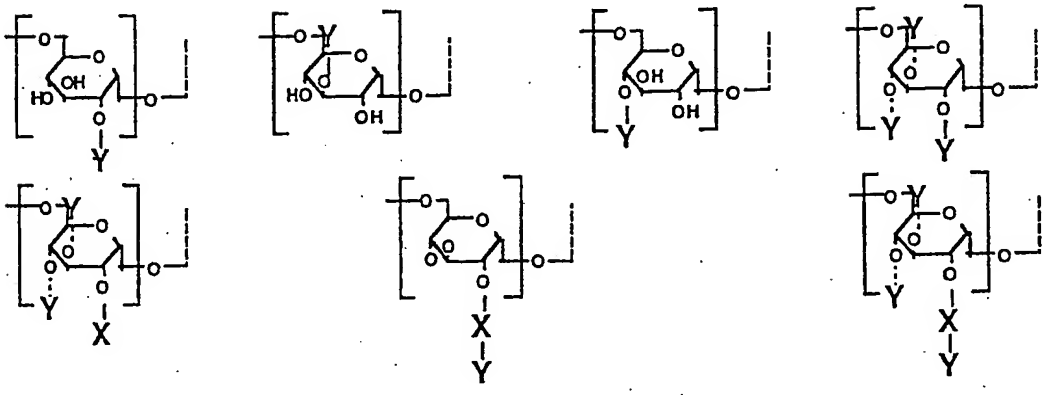
MONOMERS A



MONOMERS type A-X



MONOMERS type A-Y



MONOMERS type A-Z

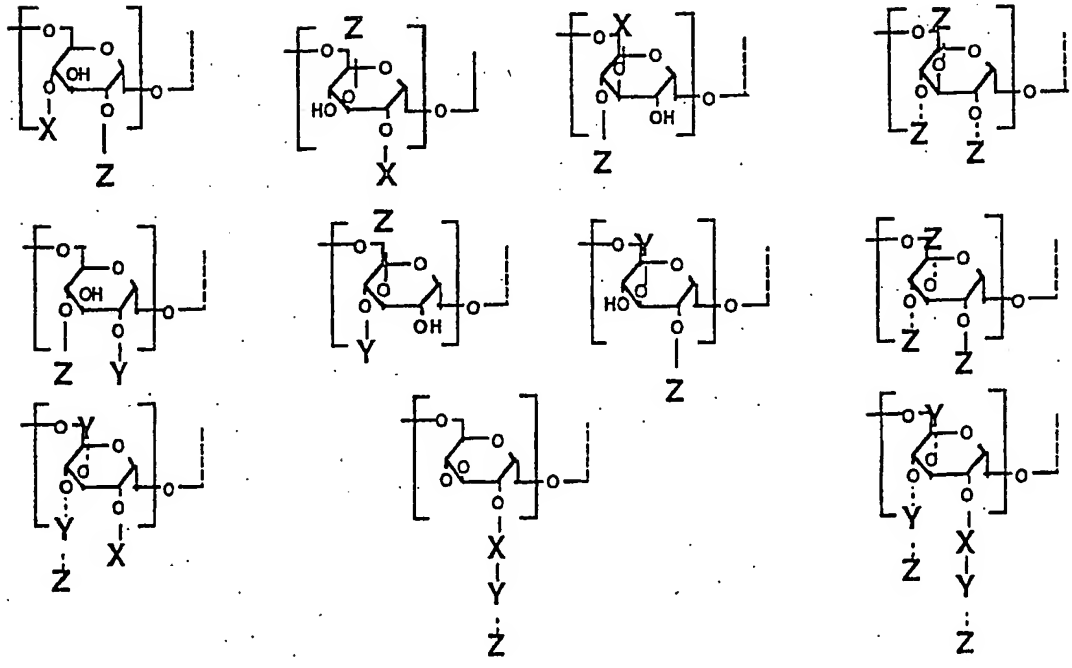


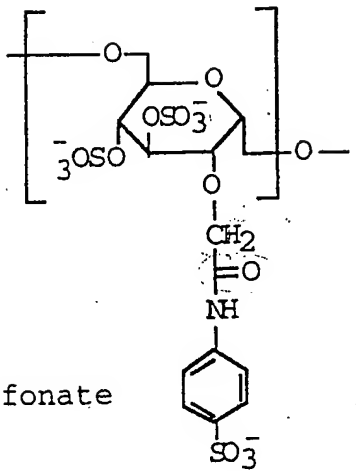
Figure 6

Reference		X = % COO^-	Y = % $SO3^-$	Z
RGTA 1000	CM_1D	48,98	0	0
RGTA 1001	$CM_1DS_{0,5}$	48,5	13,1	0
RGTA 1002	$CM_1DS_{0,75}$	44,7	25,3	0
RGTA 1003	CM_1DS_1	40,9	40,6	0
RGTA 1004	$CM_1DS_{1,5}$	31,7	56,5	0
RGTA 1005	CM_1DS_2	26,3	82,3	0
RGTA 1006	CM_1DSex	19,1	94,4	0
RGTA 1007	CM_2D	91,8	0	0
RGTA 1008	$CM_2DS_{0,5}$	84,9	18,4	0
RGTA 1009	$CM_2DS_{0,75}$	63,7	30,3	0
RGTA 1010	CM_2DS_1	61,1	37,3	0
RGTA 1011	$CM_2DS_{1,5}$	57,8	44,6	0
RGTA 1012	CM_2DS_2	55,0	55,7	0
RGTA 1013	CM_2DSex	22,6	58,5	0
RGTA 1014	CM_3D	118,3	0	0
RGTA 1015	$CM_3DS_{0,5}$	102,7	15,6	0
RGTA 1016	$CM_3DS_{0,75}$	70,9	36,5	0
RGTA 1017	CM_3DS_1	87,3	42,0	0
RGTA 1018	$CM_3DS_{1,5}$	71,2	55,0	0
RGTA 1019	CM_3DS_2	68,9	57,3	0
RGTA 1020	CM_4D	154,0	0	0
RGTA 1021	$CM_4DS_{0,5}$	114,8	8,9	0
RGTA 1022	CM_4DS_1	104,9	24,6	0
RGTA 1023	CM_4DS_2	72,2	51,8	0
RGTA 0040	DS commercial	0	97,6	0
RGTA 1024	$DS_{0,5}$ équiv	0	103,0	0
RGTA 1025	$DS_{0,25}$ équiv	0	41,4	0
RGTA 1026	$DS_{0,125}$ équiv	0	23,5	0

TABLE PRESENTING FOR EACH OF THE REFERENCED RGTA AND CORRESPONDING TO THE POLYMERS OF TYPE CM_nDS_m, THE PERCENTAGES BY DEFINITION OF FREE GROUPS X AND Y.
Z = NOTHING

Figure 7

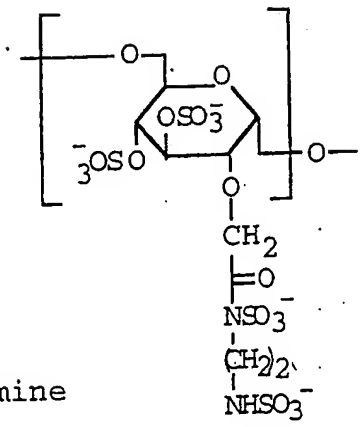
CM_2DPhSS_1



FROM p-phenylsulfonate

Figure 8

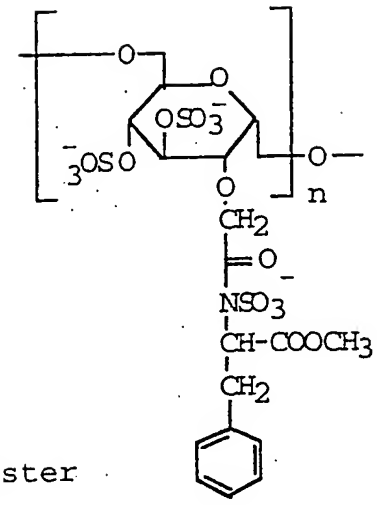
CM_2DES_1



FROM ethylenediamine

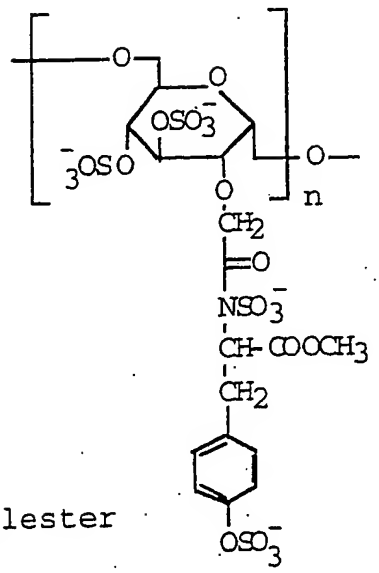
Figure 9

CM_3DPheS_2



FROM phenylalanine methylester

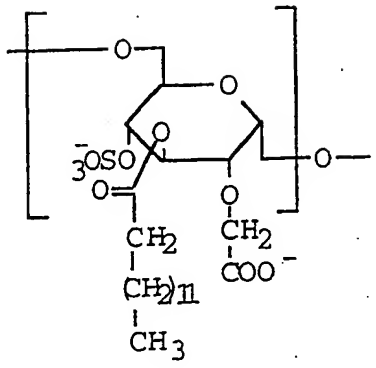
CM_3DTyrS_2



FROM tyrosine methylester

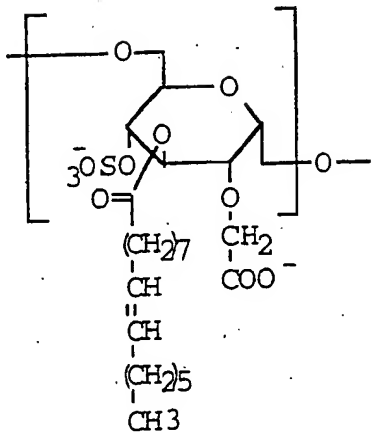
Figure 10

$CM_1DPalmS_1$



FROM PALMITIC ACID (C16)

$CM_1DOleicS_1$



FROM OLEIC CHLORIDE (C18;9)

Figure 11

Reference	polymer s	Activity OF anti-coagulant IN UI	Reference	polymer s	Activity OF anti-coagulant IN UI
Hép	Héparine	176	RGTA 1013	CM_2DSex	<50
RGTA 2010	Pcoo-	<50	RGTA 1014	CM_3D	<50
RGTA 2011	P1S	<50	RGTA 1015	$CM_3DS_{0,5}$	<50
RGTA 2012	P2S	<50	RGTA 1016	CM_3DS_1	<50
RGTA 1000	CM_1D	<50	RGTA 1017	$CM_3DS_{1,5}$	<50
RGTA 1001	$CM_1DS_{0,5}$	<50	RGTA 1019	CM_3DS_2	<50
RGTA 1002	$CM_1DS_{0,75}$	<50	RGTA 1110	$CM_2DPhSS1$	<50
RGTA 1003	CM_1DS_1	<50	RGTA 1111	CM_2DES1	<50
RGTA 1004	$CM_1DS_{1,5}$	<50	RGTA 1112	$CM_2DPheS2$	<50
RGTA 1005	CM_1DS_2	<50	RGTA 1113	$CM_3DTyrS2$	<50
RGTA 1006	CM_1DSex	<50	RGTA 1114	$CM_1DPalmS1$	<50
RGTA 1007	CM_2D	<50	RGTA 1115	$CM_1DOléicS1$	<50
RGTA 1008	$CM_2DS_{0,5}$	<50	RGTA 0040	DS commercial	<50
RGTA 1009	$CM_2DS_{0,75}$	<50	RGTA 1024	$DS_{0,5}$ équiv	<50
RGTA 1010	CM_2DS_1	<50	RGTA 1025	$DS_{0,25}$ équiv	<50
RGTA 1011	$CM_2DS_{1,5}$	<50	RGTA 1026	$DS_{0,125}$ équiv	<50
RGTA 1012	CM_2DS_2	<50	RGTA 0001	Dextran T40	<50

ANTICOAGULANT ACTIVITIES OF THE POLYMERS

Figure 12

TREATMENT	20° C	20° C	20° C	20° C	37° C	37° C
VALUE ED50 à	0 DAYS	1 DAYS	7 DAYS	15 DAYS	1 DAYS	7 DAYS
FGF1 ABOVE	6	8	14	>20	7	>20
FGF1 +Héparine	0,8	1,2	6	16	1,4	15
FGF1 + Dextran T40	6	10	>20	>20	7	>20
FGF1 + DS commercial	6	8	>20	>20	7	>20
FGF1 + $DS_{0,5}$ équiv	6	8	>20	>20	7	>20
FGF1 + $DS_{0,125}$ équiv	6	10	>20	>20	7	>20
Pcoo-	8	>20	>20	>20	18	>20
P1S	3	6	10	17	5	15
P2S	1	3	9	14	3	11
FGF1 + CM_1D	6	9	>20	>20	7	>20
FGF1 + CM2D	6	7	>20	>20	7	>20
FGF1 + CM1DS2	0,5	1,1	6	17	2,1	16
FGF1 + CM2DS2	2	8	15	>20	5	>20
FGF1 + CM_2DPhS	8	15	>20	>20	8	>20
FGF1 + $CM_2DPhSS1$	2	6	18	>20	3	14
FGF1 + CM_2DES1	1	3	8	17	9	>20
FGF1 + $CM_2DPheS2$	0,9	2	4	13	8	17
FGF1 + $CM_3DTyrS2$	3	5	>20	>20	9	>20
FGF1 + $CM_1DPalmS1$	4	4	16	>20	14	>20

STABILIZING EFFECTS OF THE POLYMERS ON FGF1

Figure 13

Reference polymer s	Conditions	concentrations (µg/ml)	ED50 FGF1 (ng/ml)	ED50 FGF2 (pg/ml)
	FGF ALONE	0	8	56
	héparino	1	2	35
RGTA 2010	Pcoo-	100	4	56
RGTA 2011	P1S	100	2.5	38
RGTA 2012	P2S	100	4	41
RGTA 0040	DS commercial	100	3	30
RGTA 1024	$DS_{0,5}$ équiv	100	4	36
RGTA 1026	$DS_{0,125}$ équiv	100	6	48
RGTA 1000	CM_1D	10	12	168
RGTA 1007	CM2D	10	16	297
RGTA 1005	CM1DS2	10	1	40
RGTA 1012	CM2DS2	10	1,5	31
RGTA 1110	CM_2DPhS1	10	8	53
RGTA 1111	CM_2DES1	10	5	45
RGTA 1112	$CM_2DPheS2$	10	3	38
RGTA 1113	$CM_3DTyrS2$	10	2	30
RGTA 1114	$CM_1DPalmS1$	10	9	42

POTENTIATION EFFECTS ON FGF1 AND FGF2.

Figure 14

	polymer + FGF2				polymer + FGF1				polymer + TGFβ			
concentration (µg/ml)	500	50	5	0.5	500	50	5	0.5	100	50	5	0.5
FGF2 ALONE	100				100				100			
FGF2 + trypsin	<1				<1				<1			
heparin (10 µg/ml)	100				100				<1			
trypsin + Pcoo-	14.4	24.4	18	22	29.7	25	18	16	5	<1	<1	<1
trypsin + P1S	61.3	100	97	87.5	85	96	100	63	58	84	70	22
trypsin + P2S	59	68	65	57	72	84	91	49	33	75	92	67

PERCENTAGE OF FGF1, FGF2 AND TGFβ NOT DEGRADED BY TRYPSIN IN THE PRESENCE OF THE POLY (β-MALIC ACID) POLYMERS

Figure 15

	% protection OF THE FACTORS			% protection OF THE FACTORS	
Polymer s	FGF2	TGFβ	Polymer s	FGF2	TGFβ
Héparin	100	15	CM_3D	22	23
CM_1D	20	25	$CM_3DS_{0,5}$	29	32
$CM_1DS_{0,5}$	74	65	CM_3DS_1	32	38
$CM_1DS_{0,75}$	77	71	$CM_3DS_{1,5}$	35	40
CM_1DS_1	80	75	CM_3DS_2	40	47
$CM_1DS_{1,5}$	96	78	$CM_2DPhSS1$	76	67
CM_1DS_2	100	80	CM_2DES1	81	71
CM_1DSex	100	81	$CM_2DPheS2$	67	56
CM_2D	20	25	$CM_3DTyrS2$	83	54
$CM_2DS_{0,5}$	87	74	$CM_1DPalmS1$	67	74
$CM_2DS_{0,75}$	90	77	$CM_1DOléicS1$	58	72
CM_2DS_1	97	80	DS commercial	87	12
$CM_2DS_{1,5}$	95	79	$DS_{0,5}$ équiv	66	9
CM_2DS_2	90	80	$DS_{0,125}$ équiv	51	10
CM_2DSex	88	74	Dextran T40	6	5

PERCENTAGE OF FGF2 & FGFβ NOT DEGRADED BY TRYPSIN IN THE PRESENCE OF THE POLYMERS DERIVED FROM DEXTRANS

Figure 16

	IC 50	mg/ml		IC 50	mg/ml
Polymèr s	Elastase	plasmin	Polymer s	Elastase	plasmin
Héparin	1,8	1	CM_2DSex	5	0,07
Pcoo-	100	53	CM_3D	>100	>100
P1S	2	0,98	$CM_3DS_{0,5}$	8	6
P2S	4,7	0,82	CM_3DS_1	6	6
CM_1D	>100	>100	$CM_3DS_{1,5}$	4	6
$CM_1DS_{0,5}$	37	8	CM_3DS_2	2	1,5
$CM_1DS_{0,75}$	24	2,5	CM_2DPhS1	12	2,4
CM_1DS_1	20	1	CM_2DES1	18	3,8
$CM_1DS_{1,5}$	3	0,15	$CM_2DPheS2$	4	0,3
CM_1DS_2	1	0.08	$CM_3DTyrS2$	1,8	0,15
CM_1DSex	1	0,035	$CM_1DPalmS1$	1,4	6
CM_2D	>100	>100	$CM_1DOléicS1$	2	9
$CM_2DS_{0,5}$	7	1	DS commercial	>100	>100
$CM_2DS_{0,75}$	5	0,7	$DS_{0,5}$ équiv	>100	>100
CM_2DS_1	2	0,5	$DS_{0,25}$ équiv	>100	>100
$CM_2DS_{1,5}$	2	0,1	$DS_{0,125}$ équiv	>100	>100
CM_2DS_2	2	0,05	Dextran T40	>100	>100

INHIBITORY EFFECTS OF THE POLYMERS ON THE ACTIVITIES OF LEUKOCYTE ELASTASE AND PLASMIN

Figure 17

Products	doses µg/ml	EFFECTS IN % OF THE CONTROL	Products	doses µg/ml	EFFECTS IN % OF THE CONTROL
		100	CM1DS1	50	134
Dextran T40	10	<100		100	189
	50	<100		200	231
	100	<100	CM2D	50	<100
	200	<100		100	<100
Heparin	10	<100	CM2DS2	20	143
	50	120		50	138
	100	<100		100	191
	200	<100		200	213
DS commercial	100	112	CM3D	50	<100
	200	124		100	<100
$DS_{0,5}$ équiv	100	<100	CM3DS2	50	136
	200	121		100	147
$DS_{0,25}$ équiv	100	109		200	178
	200	125	CM_2DPhS1	50	115
$DS_{0,125}$ équiv	100	<100		100	178
	200	129		200	189
Pcoo-	50	<100	CM_2DES1	50	137
	100	<100		100	144
	200	<100		200	168
P1S	50	150	$CM_2DPheS2$	50	152
	100	199		100	196
	200	135		200	154
P2S	50	152	$CM_3DTyrS2$	50	167
	100	170		100	241
	200	177		200	203
CM1D	50	<100	$CM_1DPalmS1$	50	133
	100	<100		100	157
	200	<100		200	176

PERENTAGES OF MUSCULAR REGENERATION AFTER INJECTION OF VARIABLE DOSES OF POLYMERS

Figure 18

EXPERIMENTAL CONDITIONS	ACTIVITY OF SOD, IN ARBITRARY UNITS
SOD CONTROL at pH = 7	100
50 microg/mL of CM1DS2 + SOD at pH = 7	132
250 microg/mL of CM1DS2 + SOD at pH = 7	165
500 microg/mL of CM1DS2 + SOD at pH = 7	196
50 microg/mL of CM3DTyrS2 + SOD at pH = 7	105
250 microg/mL of CM3DTyrS2 + SOD at pH = 7	122
500 microg/mL of CM3DTyrS2 + SOD at pH = 7	118
SOD CONTROL at pH = 3	20
50 microg/mL of CM1DS2 + SOD at pH = 3	65
250 microg/mL of CM1DS2 + SOD at pH = 3	115
500 microg/mL of CM1DS2 + SOD at pH = 3	130
50 microg/mL of CM3DTyrS2 + SOD at pH = 3	85
250 microg/mL of CM3DTyrS2 + SOD at pH = 3	133
500 microg/mL of CM3DTyrS2 + SOD at pH = 3	150
SOD CONTROL at pH = 11	30
50 microg/mL of CM1DS2 + SOD at pH = 11	40
250 microg/mL of CM1DS2 + SOD at pH = 11	95
500 microg/mL of CM1DS2 + SOD at pH = 11	122
50 microg/mL of CM3DTyrS2 + SOD at pH = 11	65
250 microg/mL of CM3DTyrS2 + SOD at pH = 11	93
500 microg/mL of CM3DTyrS2 + SOD at pH = 11	110

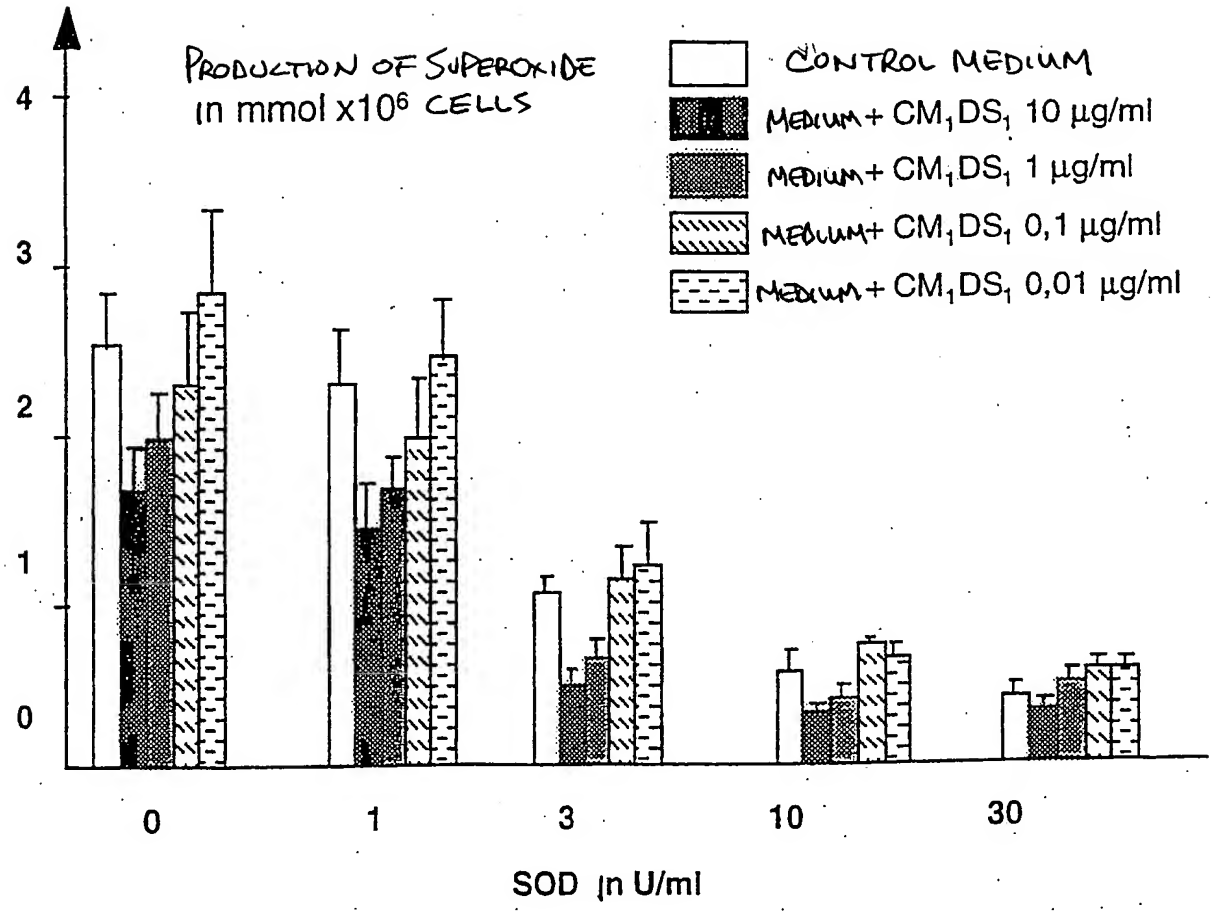
MODULATION OF THE IN VITRO ACTIVITY OF SOD BY THE POLYMERS: PROTECTIVE & POTENTIATING EFFECTS OF TWO RGTA, RGTA 1005 (CM1DS2) AND RGTA 1113 (CM3DTyrS2) ON THE IN VITRO ACTIVITY OF SOD.

Figure 19

	% OF RESIDUAL ACTIVITY			% OF RESIDUAL ACTIVITY	
Polymer s 100 mg/ml	SOD + Trypsin	SOD at 60 °C	Polymer s 100 mg/ml	SOD + Trypsin	SOD at 60 °C
Rien	0	0	CM_3D	0	0
Héparine	60	45	$CM_3DS_{0,5}$	55	60
Pcoo-	0	0	CM_3DS_1	30	40
P1S	70	80	CM_3DS_2	10	20
P2S	80	80	CM_4D	0	0
CM_1D	0	0	$CM_4DS_{0,5}$	60	100
$CM_1DS_{0,5}$	90	70	CM_4DS_1	80	100
$CM_1DS_{0,75}$	100	70	$CM_2DPhSS1$	50	60
CM_1DS_1	100	90	CM_2DES1	60	80
$CM_1DS_{1,5}$	95	75	$CM_2DPheS2$	80	100
CM_1DS_2	100	85	$CM_3DTyrS2$	80	100
CM_1DSex	90	90	$CM_1DPalmS1$	75	60
CM_2D	0	0	$CM_1DOléicS1$	70	50
$CM_2DS_{0,5}$	90	55	DS commercial	20	10
CM_2DS_1	100	70	$DS_{0,5}$ équiv	30	20
$CM_2DS_{1,5}$	70	85	$DS_{0,25}$ équiv	20	0
CM_2DS_2	90	60	$DS_{0,125}$ équiv	20	0
CM_2DSex	70	40	Dextran T40	0	0

PROTECTIVE EFFECT OF THE POLYMERS ON SOD AFTER TREATMENT BY TRYPSIN AND THERMAL SHOCK

Figure 20



POTENTIATION EFFECT OF SOD PRODUCED IN VITRO BY ACTIVATED MONOCYTES

Figure 21

Polymer s	% OF RESIDUAL ACTIVITY
Dextran T40	100
CM_1D	100
$CM_1DS_{0,5}$	30
CM_1DS_1	10
$CM_1DS_{1,5}$	0
CM_1DS_2	0
CM_1DSex	20
CM_2D	100
$CM_2DS_{0,5}$	10
CM_2DS_1	0
CM_2DS_2	0
CM_2DSex	10
$CM_2DPhSS1$	10
CM_2DES1	0
$CM_2DPheS2$	0
$CM_3DTyrS2$	0
$CM_1DPalmS1$	35
$CM_1DOléicS1$	50
DS commercial	100

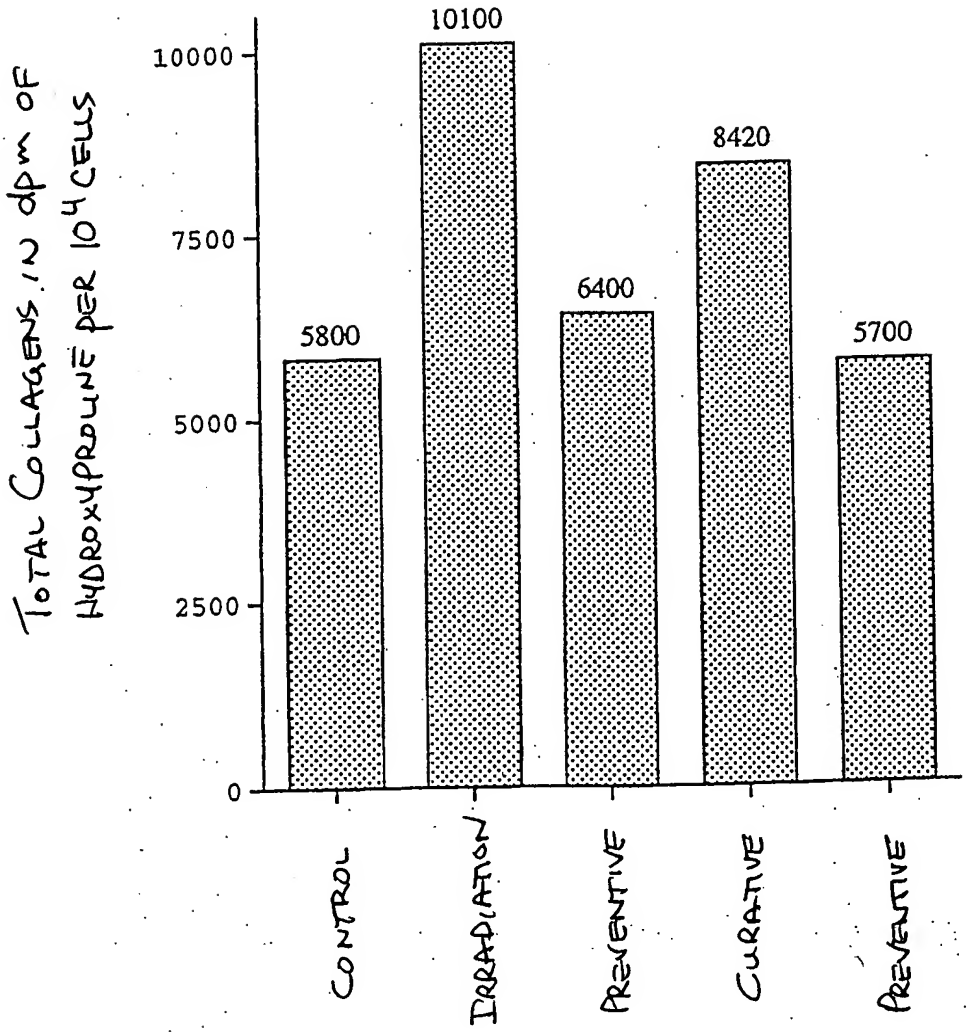
INHIBITORY EFFECTS OF THE RGTA ON CALPAINE

Figure 22

% OF RESIDUAL ACTIVITY	heparanase	% OF RESIDUAL ACTIVITY	heparanase
Dextran T40	0	CM_3D	0
CM_1D	0	$CM_3DS_{0,5}$	90
$CM_1DS_{0,5}$	60	CM_3DS_1	100
CM_1DS_1	100	CM_3DS_2	100
$CM_1DS_{1,5}$	100	CM_4D	0
CM_1DS_2	100	CM_4DS_1	75
CM_1DSex	100	CM_4DS_2	60
CM_2D	0	$CM_2DPhSS1$	80
$CM_2DS_{0,5}$	80	CM_2DES1	90
CM_2DS_1	100	$CM_2DPheS2$	100
CM_2DS_2	100	$CM_3DTyrS2$	100
CM_2DSex	100	$CM_1DPalmS1$	60
DS commercial	100	Héparine	100

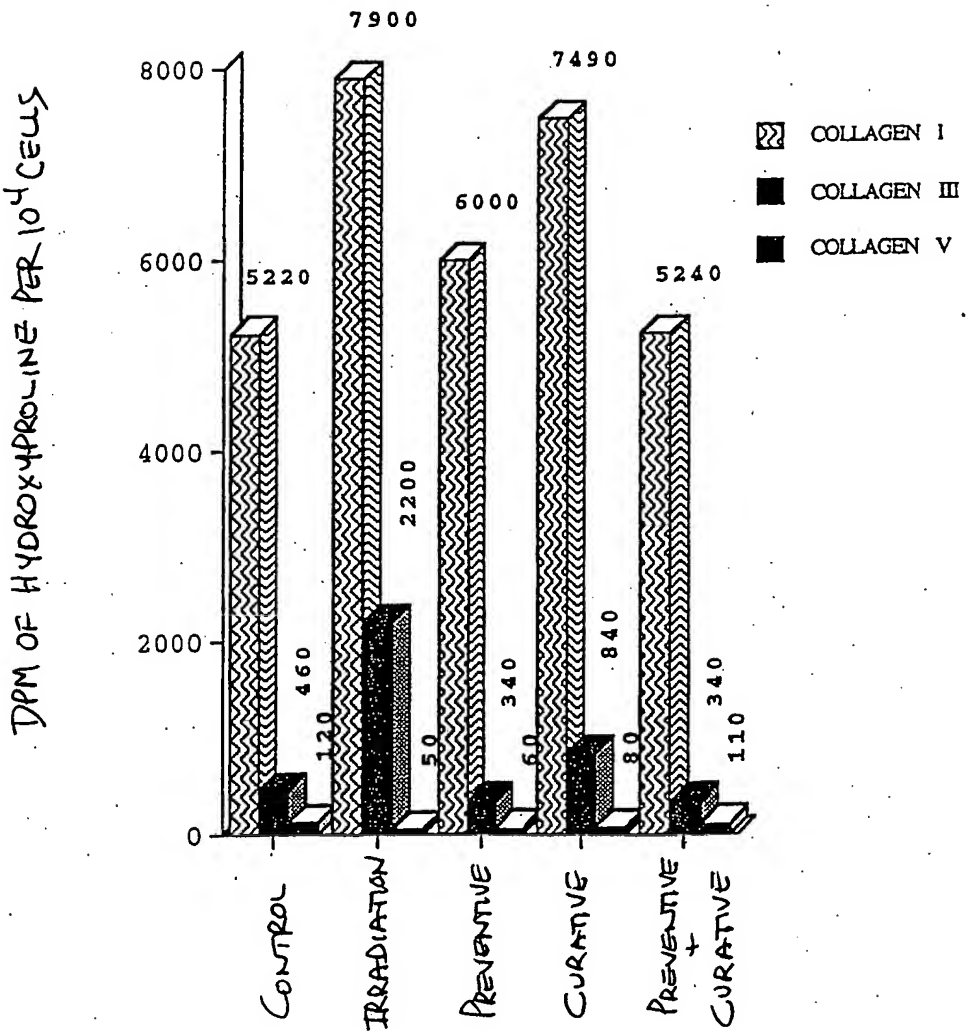
INHIBITORY EFFECTS OF THE RGTA ON HEPARITINASE

Figure 23



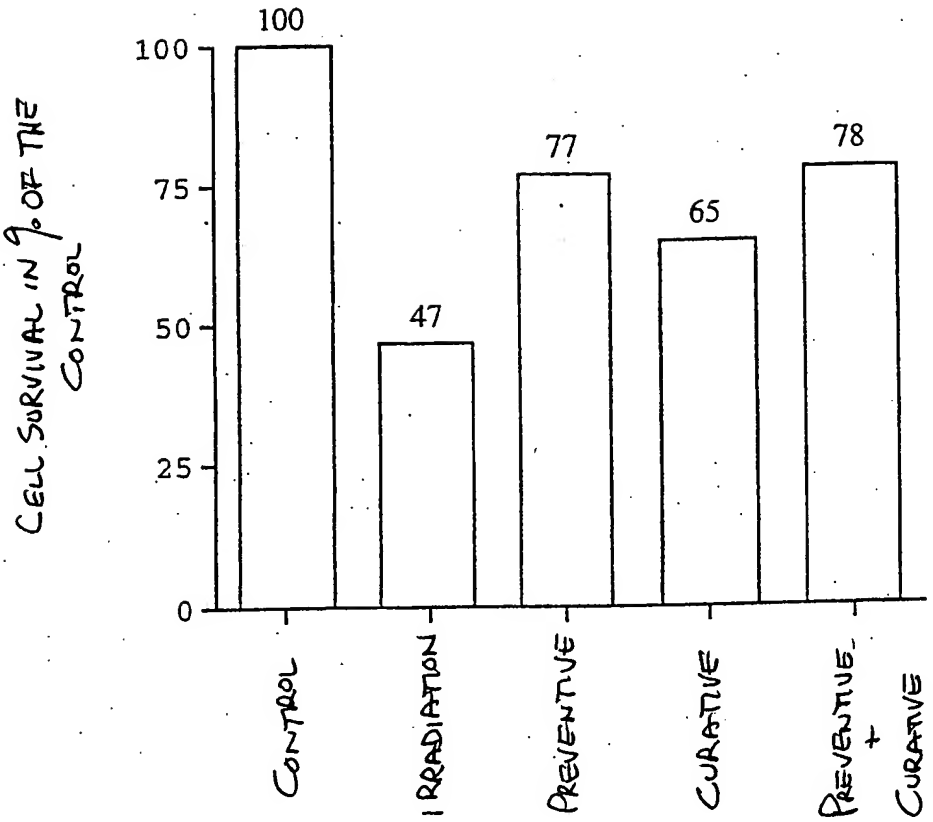
ACTIONS OF THE RGTA ON THE SECRETION OF COLLAGENS IN VITRO BY THE HISM CELLS SUBJECTED TO IONIZING RADIATION OF ^{60}Co

Figure 24



ACTION OF THE RGTA ON THE SYNTHESIS OF TYPE I, II + V COLLAGENS BY THE HSM CELLS SUBJECTED TO IONIZING RADIATION OF ^{60}Co

Figure 25



PROTECTIVE EFFECTS OF THE RGTA ON THE SURVIVAL OF CELLS SUBJECTED TO ^{60}Co IRRADIATION

Figure 26

	INHIBITON OF PROLIFERATION	IC_{50} Inhibition in µg M	(%) SYNTHESIS collagen / protein s	Collagen Type 1 IN % OF THE TOTAL 1+3+5	Collagen Type 3 IN % OF THE TOTAL 1+3+5	Collagen Type 5 IN % OF THE TOTAL 1+3+5
Dextran T40	0		17,1	58,7	36,9	4,4
CM_1D	0		17,6	59,1	35,8	5,1
CM_1DS_2	85	0,62	11,4	58,1	21,8	14,1
CM_2DS_1	75	0,47	9,3	58,7	15,8	25,5
CM_2DPheS2	85	1,12	12,1	68,5	18,5	13,0
CM_3DTyrS2	80	0,95	10,8	65,5	20,6	13,9
Heparin	82	0,36	15,5	73,0	20,9	6,1

ANTIFIBROTIC ACTION OF THE RGTA ON PIG AORTA SMOOTH MUSCLE CELLS

Fig.27

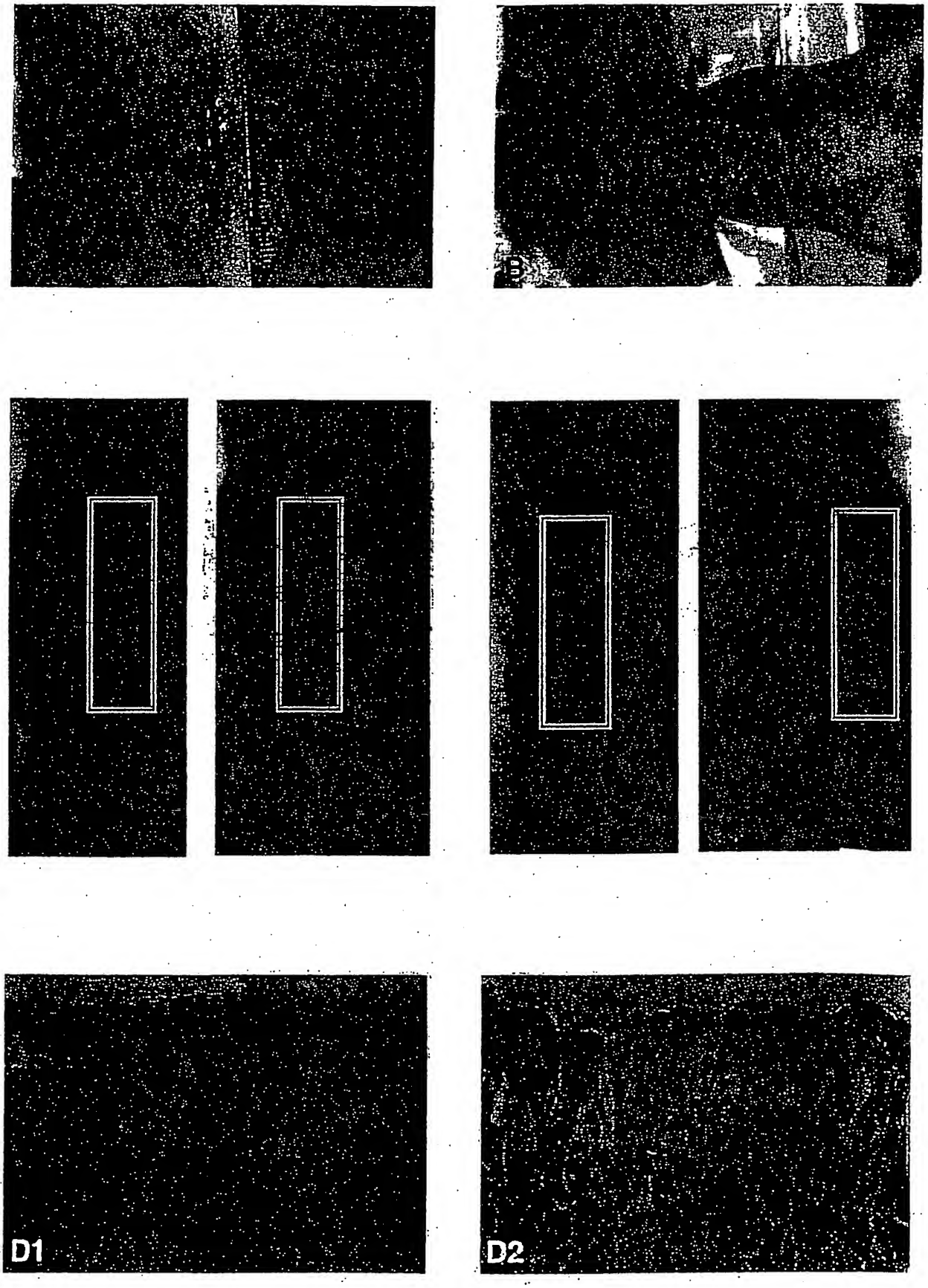


Fig.28

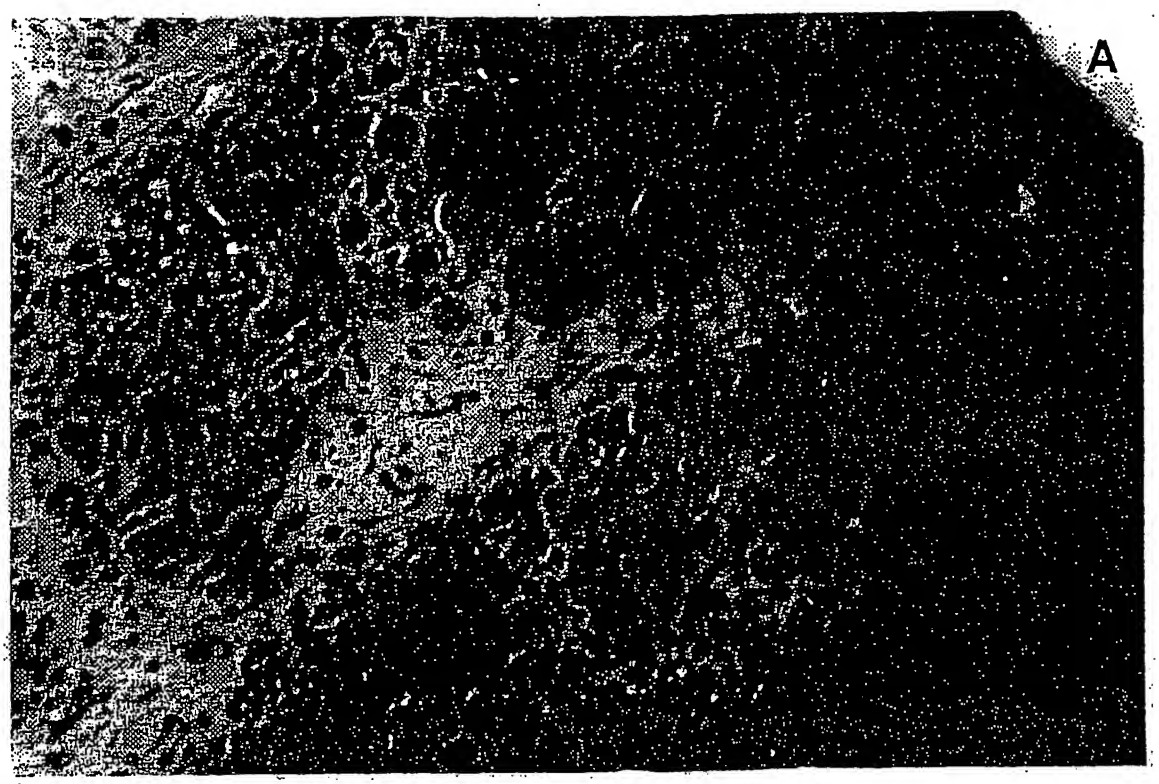


Fig.29

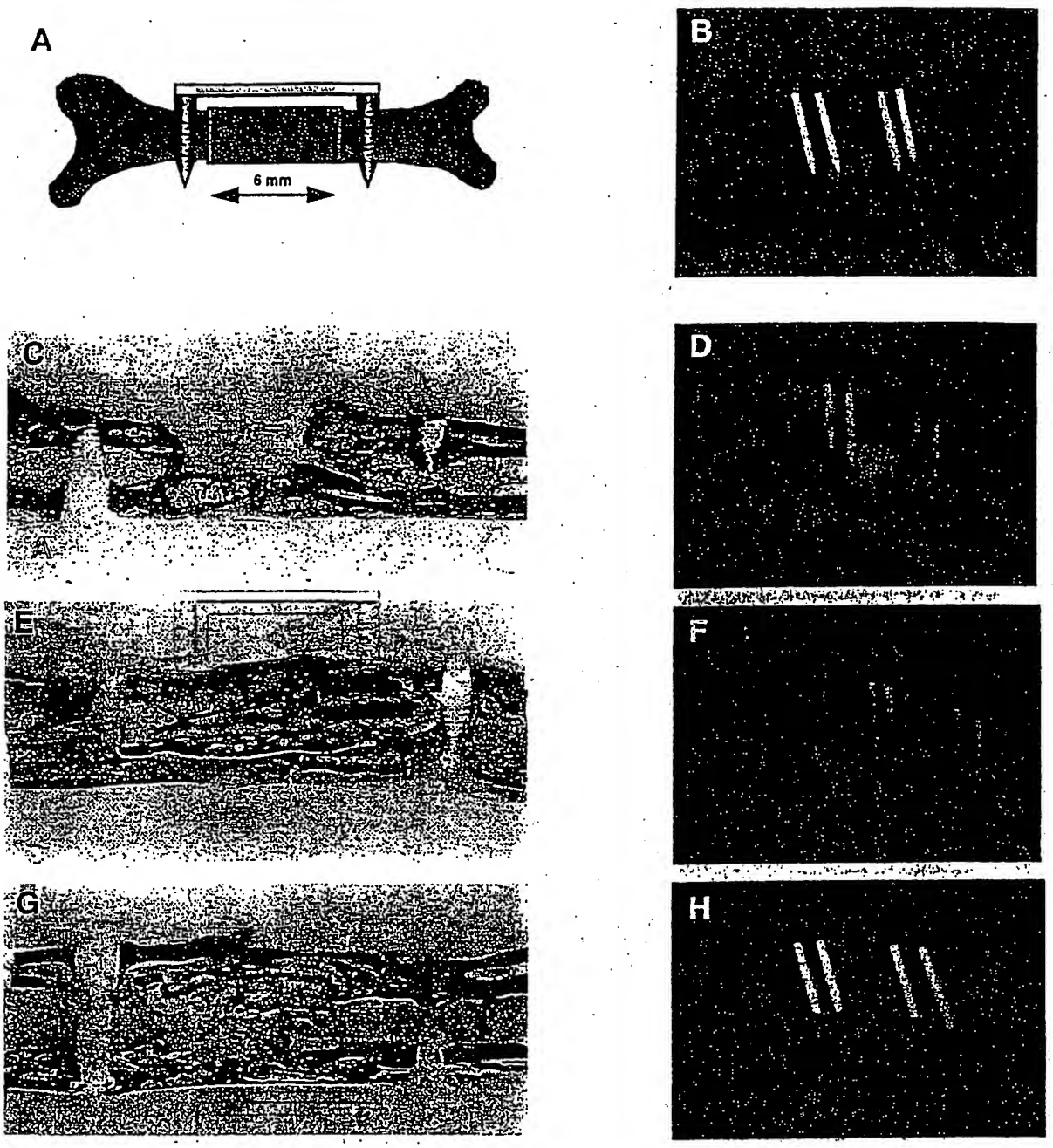
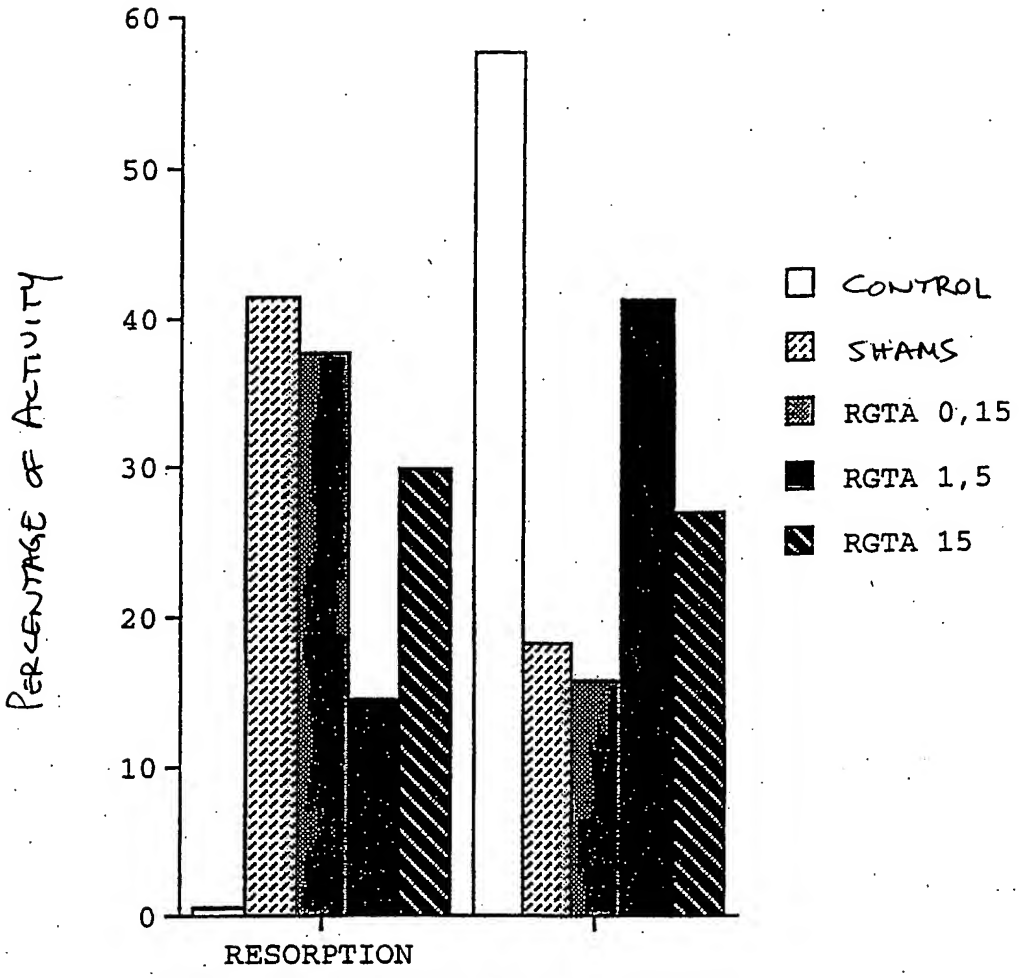


Fig.30



EFFECTS OF THE RGTA ON THE REGULATION OF THE OSSEOUS MASS AND ON THE QUALITY OF ITS RESTRUCTURING: EXAMPLE OF A CHRONIC PERIODONTAL DISEASE